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REMARKS/ARGUMENTS

Item 1: Applicants acknowledge Examiner's withdrawal of earlier rejections not reiterated in the current office action.

Rejections Under 35 U.S.C 102(b)

Items 2-3:

Claims 1-2, 4 and 6-8 were rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Chirikjian et al. This rejection is respectfully traversed. Chirikjian et al. teach methods for point mutation detection and for site-directed mutagenesis. Their output molecules are either a cleaved polynucleotide (in the case of mismatch detection, e.g. pp. 4-6) or a polynucleotide that corresponds to the sequence of either the target polynucleotide parent or the mutagenic oligonucleotide parent. The objective of Chirikjian et al. is essentially to convert one parent sequence to the other parent sequence. Chirikjian et al. do not teach the generation of polynucleotide strands with different nucleotide sequences from the parent polynucleotides as required in the instant invention. Chirikjian et al. are not motivated to make variant sequences, as they know beforehand the sequence they wish to generate. The objective of the instant invention is to generate a population of sequence variants that can be screened for a desired functional property. Such an objective is not taught or contemplated by Chirikjian et al. As Chirikjian et al. do not anticipate the instant invention, this rejection should be withdrawn.

The Examiner alleges that "the method of Chirikjian produces a polynucleotide having a different sequence from either one of at least two parents". However, the Examiner's own example demonstrates that this is not so! Specifically, if one considers the Examiner's parental sequences of:

```
5'-ATCGC-3'
   |||||
3'-TAGCG-5'
```

and

```
5'-ATYGC-3'
   |||||
3'-TGXCG-5'
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where X could be C, A or T, and Y would be the appropriate complementary base pair, and these two parents were used to generate the heteroduplex:

```
5'-ATCGC-3'
   || ||
3'-TAXCG-5'
```

and then the second parent strand was cleaved at position X, the base X removed and replaced with a nucleotide complementary to the first parent, the resulting sequence would be:

```
5'-ATCGC-3'
   |||||
3'-TAGCG-5'
```

i.e., the resulting molecule <u>is identical to the first parent.</u> Hence, the Examiner's own example demonstrates that the method of Chirikjian et al. does not teach the generation of polynucleotide strands with " a different nucleotide sequence from either of said at least two parent polynucleotides" as required in the instant claims. The reference molecules in this instance should be properly held to be the sequence of each parental strand of the heteroduplex <u>and its complement</u>. The term "sequence variant" is defined in paragraph [0093] as "a molecule (DNA, RNA polypeptide, and the like) with one or more sequence differences compared to a reference molecule", the term "parental nucleic acid" is defined in paragraph [0077] as "a nucleic acid having a sequence that is 100% identical to an original single stranded nucleic acid in a starting population of partially complementary nucleic acids", and importantly the term "identical" is defined in paragraph [0069] as" the term "identical" or "identity" means that two nucleic acid sequences have the same sequence *or a complementary sequence*" (emphasis added). Hence, generating the complementary strand to one of the parental strands comprising the heteroduplex does not constitute the generation of a "different" sequence as defined in the specification of the instant application. As Chirikjian et al. do not anticipate the instant invention, it is respectfully requested that the rejection be withdrawn.

Rejections Under 35 U.S.C 103(a)

Items 4-5:

Claim 5 was rejected under 35 U.S.C. 103(a) over Chirikjian et al. in view of Wetmur. This rejection is respectfully traversed. As detailed above, the primary reference of Chirikjian fails to teach a method of preparing a variant polynucleotide that has a different nucleotide sequence from either of said at least two parent polynucleotides as defined in the instant application. The secondary reference of Wetmur does not compensate for this basic deficiency of Chirikjian et al., hence the teaching in Wetmur of a heteroduplex comprising an entire genome is moot. Both Chirikjian et al. and Wetmur are interested in mismatch detection, and are not motivated to reassort sequence variation. According, this rejection should be withdrawn.

Items 6-7:

Claims 9-12 and 42-43 are rejected under 35 U.S.C. 103(a) over Chirikjian in view of Arnold. This rejection is respectfully traversed. The deficiencies of the primary reference Chirikjian et al. are noted above. Regarding Claims 9 and 43, Chirikjian et al. do not teach screening or selecting a population of variants for a desired functional property since they do not even generate a population of variants, but rather generate a sequence corresponding to one or the other parents. Since Chirikjian et al. generate no population of variants, there is no motivation to apply the screening or selecting technique of Arnold et al. to the method of Chirikjian et al. According, this rejection should be withdrawn.

Regarding Claim 10, Chirikjian et al. is not motivated to repeat their process since the site-directed mutagenesis process gives them the desired sequence in the first attempt.

One might be motivated to repeat the method of Chirikjian et al. to make a second site-directed mutation, but this still does not result in the instant invention, as the output molecules will still reflect the sequences of either the target polynucleotide or the mutagenic oligonucleotide. No population of variants is generated. Application of the secondary reference of Arnold et al. to motivate multiple rounds of the method of Chirikjian et al does not result in the instant invention. Accordingly, this rejection should be withdrawn.

Regarding Claims 11 and 12, again, since Chirikjian et al. do not generate a population of variants, there are no variants to convert to RNA before screening. Accordingly, this rejection should be withdrawn.

Regarding Claim 42, the deficiencies of Chirikjian et al. have been noted above. Adding the *in vitro* cell extracts from the secondary reference of Arnold et al. adds nothing to Chirikjian et al. in terms of generating a population of sequence variants. The conversion of the heteroduplex of Chirikjian et al. will still result in an output polynucleotide with a sequence corresponding to one or the other parent polynucleotide. Hence, it is respectfully requested that this rejection be withdrawn.

Items 8-10. Provisional Double Patenting. Claims 1-2, 4-12, and 42-43 are provisionally rejected over the claims of several co-pending applications. Applicants request that resolution of provisional obviousness-type double patenting matters be postponed until patentable subject matter is identified in the instant application. Such rejections could potentially be resolved, for example, *via* a terminal disclaimer.

Claims 1, 2, 4-12, 42 and 43 are now pending in the application. In view of the comments above, the rejections have been overcome. Reconsideration, withdrawal of the rejections and early indication of allowance are respectfully requested. If any issues remain, the examiner is encouraged to call the undersigned for prompt resolution.

If needed, Applicants petition for an extension of time under the provisions of 37 CFR 1.136(a) for sufficient time to accept this response. The commissioner hereby is authorized to charge payment of any fees under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No.500933.

Respectfully submitted,
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